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A Phase II Study of the Central European Society of Anticancer-Drug Research (CESAR) Group: Results of an Open-Label Study of Gemcitabine plus Cisplatin with or without Concomitant or Sequential Gefitinib in Patients with Advanced or Metastatic Transitional Cell Carcinoma of the Urothelium

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Key Words
Cisplatin · Gefitinib · Gemcitabine · Transitional cell carcinoma · Urothelial carcinoma

Abstract
Introduction: This phase II trial evaluated the efficacy and safety of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, gefitinib, in combination with first-line chemotherapy in advanced urothelial cancer. ***Methods:*** Chemotherapy-naïve patients with advanced or metastatic urothelial carcinoma were randomized 1:1:1 to receive six cycles of chemotherapy (gemcitabine 1,250 mg/m^2 on days 1 and 8, and cisplatin 70 mg/m^2 on day 1 of every cycle) concomitantly with gefitinib 250 mg/day (arm A); or with sequential gefitinib (arm B); or alone (arm C). The primary endpoint was the time to progression (TTP). ***Results:*** A total of 105 patients received study treatment. Median TTP for arms A, B, and C were 6.1, 6.3, and 7.8 months, respectively. There were no significant differences between treatment arms for any outcomes measured. The most common adverse events were nausea and vomiting. ***Conclusion:*** Gefitinib in combination with chemotherapy did not improve efficacy in advanced urothelial cancer.

Introduction

Urothelial carcinoma remains one of the leading causes of cancer mortality and morbidity in Europe [1] and the United States [2]. Approximately, 20–40% of newly diagnosed patients present with, or go on to develop, invasive disease [3]. Outcomes in these patients are particularly poor, with five-year survival rates for patients presenting with regional or distant metastases of 35 and 5%, respectively [2].

In other malignancy types, such as non-small cell lung cancer (NSCLC), breast cancer, colorectal cancer, gastrointestinal stromal tumor, and renal cell cancer, the use of targeted therapies has had a major impact in terms of improved outcomes. Over the past decade, drugs such as

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sunitinib, sorafenib, bevacizumab, imatinib, gefitinib, cetuximab, and trastuzumab have contributed to an increased clinical benefit observed in patients with cancer [4–7]. However, for patients with advanced or metastatic urothelial cancer, there are no approved targeted therapies and chemotherapy remains the standard of care [8].

The epidermal growth factor receptor (EGFR) has been implicated in the progression of urothelial carcinoma [9], and thus can be considered a potential therapeutic target. Previous studies report EGFR expression in urothelial carcinoma being in the range of 27 to 91% [10–15]. Furthermore, EGFR status has been shown to be associated with invasive disease [10] and predictive of progression and survival [12, 13, 16–18].

Gefitinib, a selective EGFR tyrosine kinase inhibitor (TKI), has shown activity in preclinical [19] and clinical [20] studies in urothelial carcinomas. In addition, the combination therapy of gefitinib with gemcitabine and cisplatin has shown activity in other tumors [21–23].

The current study was initiated to further investigate the efficacy and safety of concomitant or sequential gefitinib compared with standard chemotherapy alone in chemotherapy-naïve patients with advanced urothelial carcinoma.

Patients and Methods

Patients

Patients eligible for inclusion were ≥18 years old, having received no previous chemotherapy or other systemic antitumor therapy, estimated creatinine clearance (COCKCROFT) <60 ml/min, with histologically or cytologically confirmed, measurable, advanced, or metastatic transitional cell carcinoma of the urothelium and a World Health Organization (WHO) performance status of 0 to 1. The study was conducted from December 2003 to October 2008 in accordance with relevant local regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the ethical principles laid down in the Declaration of Helsinki [24]. All patients provided written informed consent before any study-related procedures were performed.

Study Objectives

The primary objective of the study was to assess the activity of gefitinib (250 mg) in patients with advanced or metastatic transitional cell carcinoma of the urothelium, administered once daily continuously in addition to standard chemotherapy or administered after completion of standard chemotherapy. This was measured by time to progression (TTP), based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.0. Tumor response assessments were performed by each investigator.

The secondary objectives of the study included evaluating the overall response rate (ORR), time to treatment failure (TTF), overall survival (OS), disease control rate (DCR), and duration of response. The safety objective of the study was to measure the safety and tolerability for each treatment arm. Serious adverse events (AEs) were defined as an AE that resulted in death; was life-threatening; resulted in hospitalization; resulted in prolonged disability/incapacity; or a congenital abnormality or birth defect. Patients who experienced progression or toxicity were followed up for survival until withdrawal of study medication of the last patient (study closure). Patients who withdrew were followed up every 12 weeks for survival information until death.

Study Design

This was a phase II, multicenter, open-label, randomized study of gemcitabine and cisplatin with or without concomitant or sequential gefitinib. Patients were randomized (1:1:1) into one of three arms. Across all three arms, standard chemotherapy was administered in 21-day cycles consisting of gemcitabine 1,250 mg/m^2 on days 1 and 8 and cisplatin 70 mg/m^2 on day 1. Arm A received six cycles of gemcitabine and cisplatin plus concomitant gefitinib 250 mg once daily, followed by gefitinib 250 mg once daily as maintenance therapy until tumor progression. Arm B received six cycles of gemcitabine and cisplatin followed by gefitinib 250 mg once daily until progression; and arm C received six cycles of gemcitabine and cisplatin followed by observation until progression.

An extension group, comprising patients in arm B and arm C who were unable to complete six cycles of chemotherapy either due to toxicity or objective disease progression, received gefitinib 250 mg once daily until further progression. Estimating the efficacy and safety profile of patients in the extension arm was a further exploratory endpoint.

Statistical Analysis

For the intent-to-treat (ITT) population, 102 patients (34 per treatment group) were required. Assuming a drop-out rate of approximately 20%, the sample size had to be 125 patients. The sample size was determined based on the following assumptions: 7.4 months' TTP with gemcitabine and cisplatin alone [25], corresponding to an 18-month progression-free rate of 18.5% (exponential survival function); 30% maximum benefit of additional use of gefitinib (sequentially or concomitantly), resulting in a TTP of 9.6 months (27.3% progression-free patients) in the best treatment arm. The goal was to have a probability of 75% of concluding that further evaluation of gefitinib plus gemcitabine and cisplatin on the improvement of TTP in patients with advanced or metastatic transitional cell carcinoma of the urothelium is warranted, based on the observed difference in the response rates between the treatment arms using a selection design with three arms [26].

Standard summary statistics were used to describe variables. ORRs and DCRs were summarized with proportions together with exact two-sided 95% confidence intervals (CI). Durations (TTP, OS, and duration of response) were summarized using Kaplan-Meier methods. The log-rank test was used to assess the differences between treatment arms.

Efficacy endpoints were analyzed using the ITT population. Safety endpoints were analyzed using the all-subjects-treated (AST) population.

Due to the selection design of this study, the trial was noncomparative in the strong confirmatory statistical sense. The goal of the study was to select the most efficient of the three treatment arms,

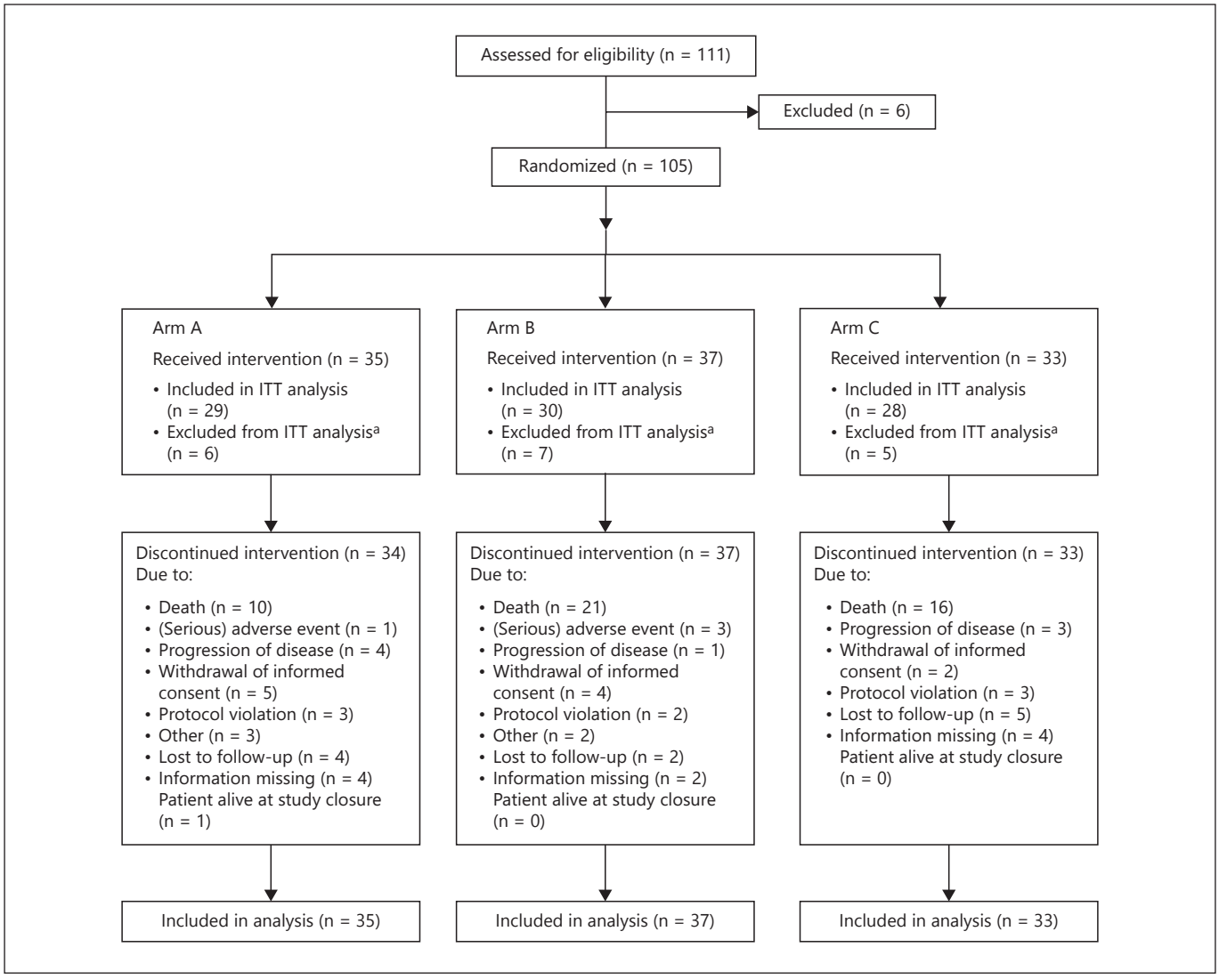

Fig. 1. CONSORT diagram. [a] Patients excluded from the ITT analysis as a result of inclusion/exclusion criteria violation (n = 3) and missing tumor assessments (n = 15) – indeterminate across all three arms. ITT = Intent-to-treat.

which would be used in a subsequent study. Despite the insufficient statistical power to assess trends in patient response to the study treatments, a log-rank test was performed for an exploratory comparison of all three target variables.

Results

Study Population

A total of 111 patients from 19 research sites in Germany and Switzerland were screened. Of these, 105 patients received study treatment (AST population). Eighteen of the 105 patients were excluded from the ITT population: three patients as a result of violation of the inclusion/exclusion criteria, and 15 patients as a consequence of missing their tumor assessment. Thus, a total of 87 patients were included in the ITT analysis (fig. 1).

Disease characteristics at baseline were representative of a population with histologically or cytologically confirmed, measurable, advanced, or metastatic transitional cell carcinoma of the urothelium. Two patients who had squamous cell histology were erroneously enrolled. The majority had metastatic disease (arm A 90%, arm B 81%, arm C 83%), and a WHO performance status of 0 or 1 (table 1). Two patients who had a WHO performance status of 2 were incorrectly enrolled.

Table 1. Baseline demographics and disease characteristics

	Number of patients (%)		
	arm A	arm B	arm C
Population, n (%)			
All patients screened	36 (100.0)	38 (100.0)	37 (100.0)
All patients treated	35 (97.2)	37 (97.4)	33 (89.2)
Intent-to-treat	29 (80.6)	30 (78.9)	28 (75.7)
Sex, n (%)			
Female	12 (34.3)	12 (32.4)	7 (21.2)
Male	23 (65.7)	24 (64.9)	26 (78.8)
Missing	0	1 (2.7)	0
Age, years			
Mean ± SD	61.8±11.3	64.7±9.5	61.4±9.7
Median	66	66	63
Range	41–84	45–80	42–78
Race, n (%)			
Caucasian	35 (100.0)	37 (100.0)	33 (100.0)
WHO performance status			
0	20 (58.8)	17 (45.9)	19 (59.4)
1	13 (38.2)	19 (51.4)	13 (40.6)
2	1 (2.9)	1 (2.7)	0
Missing	1 (2.7)	0 (0.0)	1 (2.7)
Histology, n (%)			
Transitional cell	28 (80.0)	31 (83.8)	28 (84.9)
Squamous cell	0	1 (2.7)	1 (3.0)
Adenoid	2 (5.7)	0	0
Unknown	4 (11.4)	4 (10.8)	2 (6.1)
Missing	1 (2.9)	1 (2.7)	2 (6.1)
Any tumor-related surgery			
Yes	35 (100.0)	34 (91.9)	31 (93.4)
No	0	3 (8.1)	1 (3.0)
Missing	0	0	1 (3.0)
Any tumor-related radiotherapy			
Yes	0	3 (8.1)	1 (3.0)
No	35 (100.0)	33 (89.2)	29 (87.9)
Missing	0	1 (2.7)	3 (9.1)

SD = Standard deviation; WHO = World Health Organization.

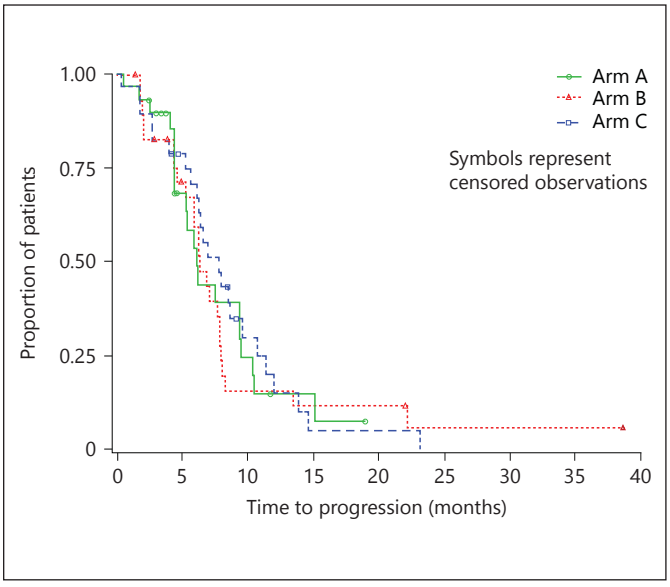

Fig. 2. Kaplan-Meier plot of time to progression.

Table 2. Response rates

	Number of patients (%)		
	arm A (n = 29)	arm B (n = 30)	arm C (n = 28)
ORR	17 (58.6)	16 (53.3)	12 (42.8)
PR	15 (51.7)	15 (50.0)	10 (35.7)
CR	2 (6.8)	1 (3.3)	2 (7.1)
SD	12 (42.8)	10 (35.7)	8 (28.5)

CR = Complete response; ORR = overall response rate; PR = partial response; SD = stable disease.

Patient demographics were generally consistent across the treatment arms; all patients were of Caucasian origin, and the majority were elderly males. Almost all patients had undergone prior surgery, with only four having received prior radiotherapy.

The most common surgery performed was transurethral resection of the bladder (41.7%). Other operations included cystectomy, nephro-urectomy, prostatectomy, and laparotomy.

In total, 19 patients (63.3%) received gefitinib in arm B after completing six cycles of chemotherapy. The extension arm included only two patients (1.9%), who were treated with gefitinib; the exploratory analysis was therefore not conducted due to the small sample size.

Efficacy Results

Median TTP for patients in arm A was 6.1 months (95% CI 4.39–9.40), in arm B 6.3 months (95% CI 5.24–7.80), and in arm C 7.8 months (95% CI 6.19–9.63). An exploratory analysis indicated that there were no statistically significant differences between the treatment arms (fig. 2).

Similarly, there were no significant differences between the treatment arms for any of the secondary endpoints. Forty-five of the 87 patients treated with gefitinib had an objective tumor response, according to RECIST criteria, comprising 40 partial responders and five complete responders. The ORRs were 58.6, 53.3, and 42.8% in arms A, B, and C, respectively (table 2).

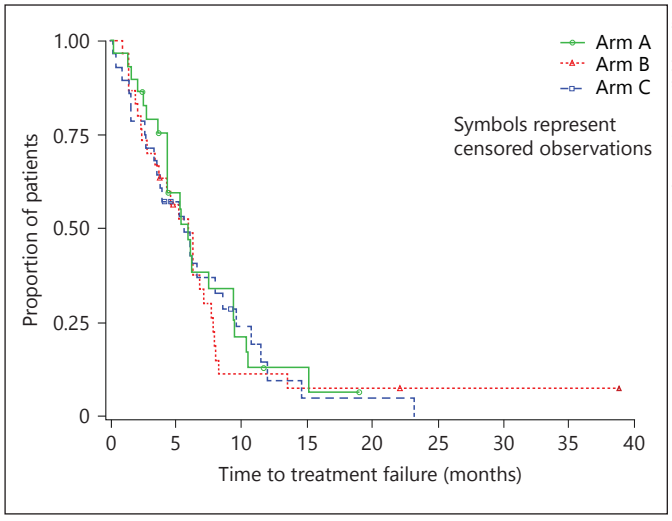

Fig. 3. Kaplan-Meier plot of time to treatment failure.

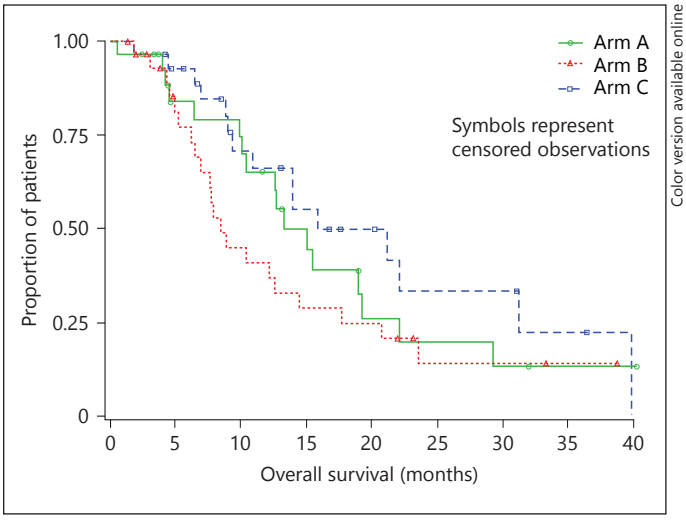

Fig. 4. Kaplan-Meier plot of overall survival.

The median TTF for patients in arms A, B, and C was 5.9 months (95% CI 4.36–9.37), 5.9 months (95% CI 3.44–7.11), and 5.6 months (95% CI 3.54–8.59), respectively (fig. 3). The median OS for patients in arm A was 13.3 months (95% CI 10.49–19.24), in arm B 8.5 months (95% CI 6.95–14.49), and in arm C 15.9 months (95% CI 10.88–31.27) (fig. 4).

Measurements of target and non-target lesions as per RECIST were performed at regular intervals (every two cycles). However, the investigator's assessment of the overall response was not collected at each individual time point. A statement of the best response achieved during the study was collected at the end of the last chemotherapy visit. Thus, the DCR and duration of response were not assessed.

Toxicity

All patients treated in the study experienced at least one AE, the most common events being nausea, vomiting, leukopenia, and fatigue. Most AEs were characterized by mild-to-moderate intensity (Common Toxicity Criteria (CTC) grades 1 and 2). There were 60 serious AEs reported in 105 patients (57.14%, AST population), the most frequent being pancytopenia, pyrexia, and vomiting (table 3).

In arm A, there were 109 AEs considered gefitinib-related, according to investigator assessment. Of these, rash (CTC grade 1 or 2) was the most common (40.0% of patients). There were 13 gefitinib-related SAEs in arm A. In arm B, 23 AEs were considered by investigators as likely to be related to gefitinib, of which diarrhea (CTC grade 1 or 2, except in one patient) was the most common (10.8% of patients). There were two gefitinib-related SAEs in arm B.

Overall, there were 152 cases of therapy delay or dose reduction due to AEs across all arms of the study. There were 17 dose interruptions, most frequently due to toxicity. There were no dose interruptions in arm C. The most common reason for study discontinuation was death: 10 patients (28.5%) in arm A; 21 patients (56.8%) in arm B; and 17 patients (51.5%) in arm C. In total, there were 61 deaths during the course of the study: 19 (54.3%), 23 (62.2%), and 19 (57.6%) in arms A, B, and C, respectively. The most common cause of death was urothelial carcinoma disease progression (17, 20, 19 in arms A, B, and C, respectively). Deaths not considered related to disease progression were caused by septic shock (one patient) and apoplexy (one patient) in arm A, and pulmonary insufficiency (one patient), cardiorespiratory failure (one patient), and unknown cause (one patient) in arm B.

Discussion

Cisplatin-based chemotherapy is the standard of care in patients with advanced urothelial carcinoma. Specifically, gemcitabine-cisplatin combination chemotherapy has been shown to provide the best efficacy and tolerability, replacing methotrexate, vinblastine, doxorubicin, and cisplatin as the treatment of choice [27]. Efforts to improve outcomes in this patient group have focused on the addition of a third drug. It has been proposed that the addition of a targeted therapeutic agent would result in im-

Table 3. Adverse events and serious adverse events regardless of causality occurring in >10% frequency in any arm

Preferred term	Number of patients[a] (%)		
	arm A (n = 35)	arm B (n = 37)	arm C (n = 33)
Any adverse event			
Alopecia	4 (11.4)	13 (35.1)	10 (30.3)
Anemia	10 (28.6)	18 (48.6)	10 (30.3)
Anorexia	5 (14.3)	6 (16.2)	6 (18.2)
Asthenia	2 (5.7)	1 (2.7)	5 (15.2)
Back pain	6 (17.1)	0	3 (9.1)
Cancer pain	1 (2.9)	4 (10.8)	2 (6.1)
Cardiac discomfort	0	4 (10.8)	0
Chills	0	0	6 (18.2)
Constipation	5 (14.3)	6 (16.2)	3 (9.1)
Cystitis	2 (5.7)	5 (13.5)	0
Diarrhea	17 (48.6)	10 (27)	5 (15.2)
Drug hypersensitivity	1 (2.9)	1 (2.7)	6 (18.2)
Epistaxis	2 (5.7)	4 (10.8)	3 (9.1)
Fatigue	8 (22.9)	25 (67.6)	27 (81.8)
General physical health deterioration	4 (11.4)	5 (13.5)	1 (3)
Hematuria	2 (5.7)	5 (13.5)	0
Hemoglobin decreased	5 (14.3)	2 (5.4)	4 (12.1)
Hemoptysis	0	5 (13.5)	0
Headache	1 (2.9)	7 (18.9)	5 (15.2)
Hyperhidrosis	0	5 (13.5)	0
Hypertension	3 (8.6)	5 (13.5)	1 (3)
Leukopenia	21 (60.0)	20 (54.1)	26 (78.8)
Nausea	31 (88.6)	34 (91.9)	36 (109.1)
Neutropenia	13 (37.1)	7 (18.9)	8 (24.2)
Pain	6 (17.1)	2 (5.4)	2 (6.1)
Pancytopenia	8 (22.9)	7 (18.9)	2 (6.1)
Pleural effusion	0	5 (13.5)	0
Pneumonia	4 (11.4)	5 (13.5)	0
Pruritus	3 (8.6)	4 (10.8)	1 (3.0)
Pyrexia	10 (28.6)	11 (29.7)	7 (21.2)
Rash	15 (42.9)	6 (16.2)	3 (9.1)
Renal failure	8 (22.9)	0	0
Stomatitis	1 (2.9)	2 (5.4)	6 (18.2)
Subclavian vein thrombosis	4 (11.4)	0	0
Thrombocytopenia	9 (25.7)	4 (10.8)	6 (18.2)
Urinary tract infection	1 (2.9)	12 (32.4)	6 (18.2)
Visual disturbance	5 (14.3)	0	0
Vomiting	23 (65.7)	20 (54.1)	25 (75.8)
Any serious adverse event			
Anemia	2 (5.7)	4 (10.8)	0
Neutropenia	4 (11.4)	0	0
Pancytopenia	5 (14.3)	7 (18.9)	0
Pleural effusion	0	4 (10.8)	0
Pneumonia	4 (11.4)	3 (8.1)	0
Pyrexia	0	4 (10.8)	3 (9.1)
Renal failure	4 (11.4)	0	0
Visual disturbance	4 (11.4)	0	0
Vomiting	5 (14.3)	1 (2.7)	2 (6.1)

[a] Patients who experienced separate adverse events of different common toxicity criteria grades may have been counted more than once.

proved efficacy and minimal toxicity, as observed in other tumor types [4–7]. Presently, there are no approved targeted therapies for urothelial carcinoma; however, a number of potential molecular targets are being investigated in clinical research, including the EGFR family, multitargeted TKIs, angiogenesis (vascular endothelial growth factor (VEGF) and VEGFR), fibroblast growth factor receptor (FGFR), RTK-Ras/Raf/MAPK, PI3K/AKT/mTOR, and anti-CTLA4 antibody (reviewed in [28–30]).

The aim of the current study was to establish whether the efficacy of the gemcitabine-cisplatin regimen would be improved with the addition of the EGFR-TKI gefitinib. This combination and dosing (gefitinib 250 mg, gemcitabine 1,250 mg/m^2) appeared to be highly active and well tolerated in a phase I study in patients with advanced solid tumors [21]. The gemcitabine dose of 1,250 mg/m^2 has also been shown to be well tolerated in patients with transitional cell carcinoma of the bladder [31, 32]. Our results did not show any significant benefits with either concomitant or sequential gefitinib, although a trend towards higher response rates was observed. In our study, the ORRs in both gefitinib arms (arms A and B) were similar to those reported in the gemcitabine-cisplatin only arm (49.4%) in a phase III trial [33] and slightly higher than those reported in a phase II trial of gemcitabine-cisplatin given concomitantly with gefitinib in patients with advanced urothelial carcinoma (58.6 and 53.3% vs. 42.6%) [34]. Unintentional selection bias may account for the comparatively low response rates. It is probable that the OS data were influenced by the nature of subsequent treatments; however, information on these treatments was not collected, and this is therefore recognized as a limitation of the OS findings.

The toxicity profiles of both gefitinib arms (arms A and B) were similar to that observed for gemcitabine-cisplatin alone (arm C). All AEs were consistent with the

tolerability profiles of the study drugs and the conditions associated with progression of urothelial carcinoma.

At the time this study was conducted, the role played by mutations in the *EGFR* gene in the response to gefitinib was not fully understood and *EGFR* mutation testing was not typically performed in urothelial carcinoma. Subsequently, studies in advanced NSCLC have demonstrated that certain somatic *EGFR* mutations predict for an improved tumor response to gefitinib treatment, compared with wild-type disease. Consequently, *EGFR* mutation testing is now part of routine investigations in advanced NSCLC [35, 36].

A possible explanation for the lack of efficacy observed in the gefitinib arms in comparison with the control arm in the current study could be due to the absence of *EGFR* mutations conferring sensitivity to EGFR-TKI; however, as retrospective testing is not possible, this cannot be verified. In addition, EGFR-TKI-sensitizing mutations in urothelial carcinoma are thought to be extremely rare – a number of studies investigating this tumor type have been unable to determine their existence [37–41]. Preclinical studies in urothelial carcinoma have found that the tumor cell-growth inhibition effect of gefitinib is independent of both the mutation status and protein level of EGFR [37, 42]. Inoue et al. also suggested that upregulation of YY1 and *E-cadherin* may be implicated in gefitinib-sensitivity observed in certain bladder cancer cell lines [42]. In addition, uncoupling of mitogenic pathways downstream of EGFR, due to PDGFRβ activation, has been shown to cause resistance to gefitinib in bladder cancer cell lines [43].

Targeting multiple pathways in order to improve treatment outcomes in advanced urothelial cancer has also been suggested. Several studies have proposed that co-expression patterns of EGFR alongside other members of the EGFR super-family or the tyrosine kinase recepteur d'origine nantais (RON) may be a better prognostic indicator than any of the receptors alone in urothelial carcinoma [15, 44, 45]. Hsu et al. have also presented clinical evidence that EGFR and RON are able to activate one another in bladder cancer cell lines [45]. Conflicting results have been reported for the VEGFR and EGFR dual inhibitor vandetanib. Greater antitumor activity was exhibited for vandetanib than gefitinib in human bladder cancer cell lines, and vandetanib also displayed synergism with cisplatin [39]. However, vandetanib in combination with docetaxel did not exhibit a significant improvement in progression-free survival in patients with advanced urothelial cancer [46].

Data indicate that radical treatment of the tumor, even in a metastatic setting, may improve outcomes [47], and it would be interesting to investigate whether there were differences in findings between the patients who received transurethral resection, radical cystectomy, and radiation alone. Unfortunately, this was not a planned outcome for this study and the data are not available; however, it is recommended that this analysis should be included in future trials of this nature.

In summary, gefitinib did not contribute to better patient outcomes in this population of metastatic urothelial carcinoma; platinum-based chemotherapy remains the cornerstone of treatment. However, it is hoped that by gaining a better understanding of the different molecular pathways that influence disease progression in this tumor indication, more effective targeted therapies may be developed. An assessment of EGFR status would be of potential value in future studies of EGFR/TKIs in urothelial carcinoma; identification of patients that is most likely to benefit from these therapies may also result in improved clinical outcomes.

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